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(54) **PESTICIDAL ACTIVITY OF FUNCTIONALIZED ALKENES**

FUNKTIONALISIERTE ALKENEN MIT PESTIZIDE AKTIVITÄT

ACTIVITE PESTICIDE D'ALCENES FONCTIONNALISES

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EP 1 241 941 B1

Description

Field of the Invention

[0001] The present invention concerns functionalized alkenes, along with alkane and alkyne analogs thereof, that have pesticidal activity, along with methods of use thereof.

Background of the Invention

[0002] Many blood-ingesting pests are known to feed on humans and animals, and many pests are vectors for pathogenic microorganisms which threaten human and animal health, including commercially important livestock, pets and other animals. Various species of mosquitoes, for example, transmit diseases caused by viruses, and many are vectors for disease-causing nematodes and protozoa. Mosquitoes of the genus *Anopheles* transmit Plasmodium, the protozoan which causes malaria, a devastating disease which results in approximately 1 million deaths annually. The mosquito species *Aedes aegypti* transmits an arbovirus that causes yellow fever in humans. Other arboviruses transmitted by *Aedes* species include the causative agents of dengue fever, eastern and western encephalitis, Venezuelan equine encephalitis, St. Louis encephalitis, chikungunya, oroponehe and bunyarnidera. The genus *Culex,* which includes the common house mosquito *C. pipiens*, is implicated in the transmission of various forms of encephalitis and filarial worms. The common house mosquito also transmits *Wuchereria banuffi* and *Brugia malayi*, which cause various forms of lymphatic filariasis, including elephantiasis. *Trypanasomas cruzi*, the causative agent of Chagas' disease, is transmitted by various species of blood-ingesting Triatominae bugs. The tsetse fly (*Glossina* spp.) transmits African trypanosomal diseases of humans and cattle. Many other diseases are transmitted by various blood-ingesting pest species. The order Diptera contains a large number of blood-ingesting and disease-bearing insects, including, for example, mosquitoes, black flies, no-see-ums (punkies), horse flies, deer flies and tsetse flies.

[0003] Various pesticides have been employed in efforts to control or eradicate populations of disease-bearing pests, such as disease-bearing blood-ingesting pests. For example, DDT, a chlorinated hydrocarbon, has been used in attempts to eradicate malaria-bearing mosquitoes throughout the world. Other examples of chlorinated hydrocarbons are BHC, lindane, chlorobenzilate, methoxychlor, and the cyclodienes (e.g., aldrin, dieldrin, chlordane, heptachlor, and endrin). The long-term stability of many of these pesticides and their tendency to bioaccumulate render them particularly dangerous to many non-pest organisms.

[0004] Another common class of pesticides is the organophosphates, which is perhaps the largest and most versatile class of pesticides. Organophosphates include, for example, parathion, Malathion, diazinon, naled, methyl parathion, and dichlorvos. Organophosphates are generally much more toxic than the chlorinated hydrocarbons. Their pesticidal effect results from their ability to inhibit the enzyme cholinesterase, an essential enzyme in the functioning of the insect nervous system. However, they also have toxic effects on many animals, including humans.

[0005] The carbamates, a relatively new group of pesticides, include such compounds as carbamyl, methomyl, and carbofuran. These compounds are rapidly detoxified and eliminated from animal tissues. Their toxicity is thought to involve a mechanism similar to the mechanism of the organophosphates; consequently, they exhibit similar shortcomings, including animal toxicity.

[0006] A major problem in pest control results from the capability of many species to develop pesticide resistance. Resistance results from the selection of naturally-occurring mutants possessing biochemical, physiological or behavioristic factors that enable the pests to tolerate the pesticide. Species of *Anopheles* mosquitoes, for example, have been known to develop resistance to DDT and dieldrin. DDT substitutes, such as Malathion™, propoxur and fenitrothion are available; however, the cost of these substitutes is much greater than the cost of DDT.

[0007] There is clearly a longstanding need in the art for pesticidal compounds that are pest-specific, that reduce or eliminate direct and/or indirect threats to human health posed by presently available pesticides, that are environmentally compatible in the sense that they are biodegradable, are not toxic to non-pest organisms, and have reduced or no tendency to bioaccummulate.

[0008] Many pests, including for example blood-imbibing pests, must consume and digest a proteinaceous meal to acquire sufficient essential amino acids for growth, development and the production of mature eggs. Adult pests, such as adult mosquitoes, need these essential amino acids for the production of vitellogenins by the fat body. These vitellogenins are precursors to yolk proteins which are critical components of oogenesis. Many pests, such as house flies and mosquitoes, produce oostatic hormones that inhibit egg development by inhibiting digestion of the protein meal and thereby limiting the availability of the essential amino acids necessary for egg development.

[0009] Serine esterases such as trypsin and trypsin-like enzymes (collectively referred to herein as "TTLE") are important components of the digestion of proteins by insects. In the mosquito, *Aedes aegypti*, an early trypsin that is found in the midgut of newly emerged females is replaced, following the blood meal, by a late trypsin . A female mosquito typically weighs about 2 mg and produces 4 to 6 ug of trypsin within several hours after ingesting a blood meal. Con-

tinuous boisynthesis at this rate would exhaust the available metabolic energy of a female mosquito; as a result, the mosquito would be unable to produce mature eggs, or even to find an oviposition site. To conserve metabolic energy, the mosquito regulates TTLE biosynthesis with a peptide hormone named Trypsin Modulating Oostatic Factor (TMOF). Mosquitoes produce TMOF in the follicular epithelium of the ovary 12-35 hours after a blood meal; TMOF is then released into the hemolymph where it binds to a specific receptor on the midgut epithelial cells, signaling the termination of TTLE biosynthesis. This regulatory mechanism is not unique for mosquitoes; flesh flies, fleas, sand flies, house flies, dog flies and other insect pests which need protein as part of their diet have similar regulatory mechanisms.

[0010] In 1985, Borovsky purified an oostatic hormone 7,000-fold and disclosed that injection of a hormone preparation into the body cavity of blood imbibed mosquitoes caused inhibition of egg development and sterility (Borovsky, D. [1985] *Arch. Insect Biochem. Physiol.* 2:333-349). Following these observations, Borovsky (Borovsky, D. [1988] *Arch. Ins. Biochem. Physiol.* 7:187-210) reported that injection or passage of a peptide hormone preparation into mosquitoes inhibited the TTLE biosynthesis in the epithelial cells of the gut. This inhibition caused inefficient digestion of the blood meal and a reduction in the availability of essential amino acids translocated by the hemolymph, resulting in arrested egg development in the treated insect. Borovsky observed that this inhibition of egg development does not occur when the oostatic hormone peptides are inside the lumen of the gut or other parts of the digestive system (Borovsky, D. [1988], *supra).*

[0011] Following the 1985 report, the isolated hormone, (a ten amino acid peptide) and two TMOF analogues were disclosed in U.S. Patent Nos. 5,011,909 and 5,130,253, and in a 1990 publication (Borovsky et al. [1990] *FASEB J.* 4: 3015-3020). Additionally, U.S. Patent No. 5,358,934 discloses truncated forms of the full length TMOF which have prolines removed from the carboxy terminus, including the peptides YDPAP, YDPAPP, YDPAPPP, and YDPAPPPP.

[0012] D. Borovsky and R. Linderman, U.S. Patent Application Serial No. 09/295,996, filed April 21, 1999 (WO-A-0 063 233), discloses additional novel peptides and the use thereof to control insect pests.

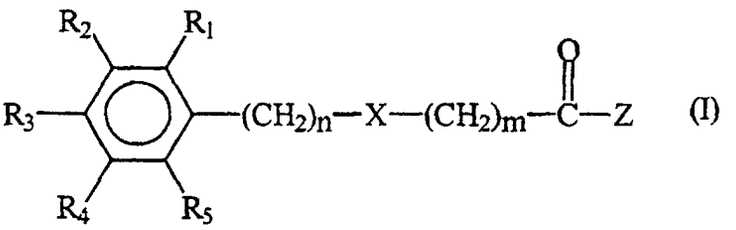
[0013] TMOF analogs that have been identified to date are primarily peptide analogs. In order to provide a greater diversity of new pesticidal compounds, it would be desirable to possess compounds that are TMOF analogues, yet are not peptides.

Summary of the Invention

[0014] The present invention is based on the discovery of non-peptide organic compounds that have a structure analogous to or reminiscent of the TMOF structure and have pesticidal activity. Thus the present invention concerns pesticidal compounds that inhibit digestion in pests by terminating or otherwise blocking synthesis of digestive enzymes by activating a TMOF receptor (collectively referred to herein as "pesticidal compounds"). The pesticidal compounds and other compounds of the present invention are usefully employed in the control of pests, particularly insect pests such as mosquitoes, which ingest blood.

[0015] Thus, a first aspect of the present invention is a method of controlling a pest such as an insect pest, comprising administering to said pest a pesticidally effective amount of a non-peptide TMOF analog (that is, an organic compound that has TMOF activity). This definition is specifically intended to exclude the peptide TMOF agonists or analogs disclosed in, *inter alia*, U.S. Patents Nos. 5,011,909; 5,130,253; and 5,358,934.

[0016] Particular pesticidal compounds/non-peptide TMOF analogs of the present invention have the formula I below:



(I)

wherein:

X is selected from the group consisting of -CHCH-, -CH_2CH_2-, and -CC-;
Z is selected from the group consisting of -OH, -NH_2 and -OR_6 wherein R_6 is loweralkyl;
n and m are each at least 1 and together total an integer from 2, 3 or 4 to 6, 8, 10 or 12; and
R_1, R_2, R_3, R_4, and R_5 are each independently selected from the group consisting of-H, -OH, halo, loweralkyl, and loweralkoxy; subject to the proviso that:
a pair of R_1 and R_1, R_2 and R_3, or R_3 and R_4 on the phenyl ring may together represent -CR_7=CR_8-CR_9=CR_{10}-,

to form with the phenyl ring illustrated above a naphthyl ring system, wherein R_7, R_8, R_9, and R_{10} are each independently selected from the group consisting of -H, -OH, halo, loweralkyl, and loweralkoxy.

[0017] A second aspect of the present invention is a method of initiating a TMOF receptor-mediated biological response. The method comprises contacting to a TMOF receptor *in vivo* or *in vitro* for a time and in an amount sufficient to initiate a TMOF receptor-mediated biological response a compound of Formula I as described herein. The biological response may be any suitable biological response mediated by the TMOF receptor, including but not limited to inhibition of biosynthesis of a digestive enzyme such as trypsin.

[0018] As noted above, the pesticidal compounds of the present invention have advantageous biological activity against pests. The novel compounds of the invention are particularly active against blood-sucking insects, particularly against species of mosquitoes such as *Aedes aegypti* that are common vectors of arthropod-borne viral diseases, such as arboviruses. Other biting pests such as flies, fleas, ticks, and lice can also be controlled using compounds and methods of the subject invention. These pests utilize TTLE as their primary blood-digesting enzymes.

[0019] The subject compounds can also be used to control pests of agricultural crops, for example by applying the compounds to the agricultural crops. These pests include, for example, coleopterans (beetles), lepidopterans (caterpillars), and mites. The compounds of the subject invention can also be used to control household pests including, but not limited to, ants and cockroaches.

[0020] Another aspect of the subject invention pertains to a method for controlling pests, particularly insect pests, comprising administering to said pest a pesticidally effective amount of a pesticidal compound of the subject invention.

[0021] The subject invention provides pest control compositions comprising pesticidal compounds and a suitable pesticidal carrier. The pest control compositions are formulated for application to the target pests or their situs.

[0022] The methods and materials of the subject invention provide a novel approach to controlling insects and insect-transmitted diseases. The compounds of the subject invention have advantageous activity and increased resistance to proteolysis over previously disclosed compounds.

Detailed Description of the Preferred Embodiments

[0023] As used herein, the term "pesticidally effective" is used to indicate an amount or concentration of a pesticidal compound which is sufficient to reduce the number of pests in a geographical locus as compared to a corresponding geographical locus in the absence of the amount or concentration of the pesticidal compound.

[0024] The term "pesticidal" is not intended to refer only to the ability to kill pests, such as insect pests, but also includes the ability to interfere with a pest's life cycle in any way that results in an overall reduction in the pest population. For example, the term "pesticidal" includes inhibition of a pest from progressing from one form to a more mature form, e.g., transition between various larval instars or transition from larva to pupa or pupa to adult. Further, the term "pesticidal" is intended to encompass anti-pest activity during all phases of a pest's life cycle; thus, for example, the term includes larvacidal, ovicidal, and adulticidal activity.

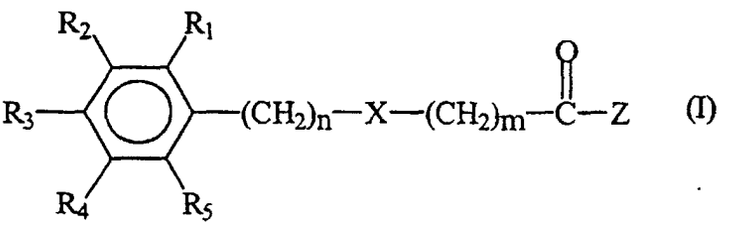
[0025] The term "loweralkyl" as used herein means C_1 to C_4 alkyl, preferably methyl, ethyl or propyl.

[0026] The term "loweralkoxy" as used herein means C_1 to C_4 alkoxy, preferably methoxy, ethoxy, or propoxy.

[0027] The term "halo" as used herein means halogen, preferably fluoro, chloro, bromo or iodo, most preferably fluoro.

1. Pesticidal compounds.

[0028] Compounds useful in the present invention have the general formula I below:



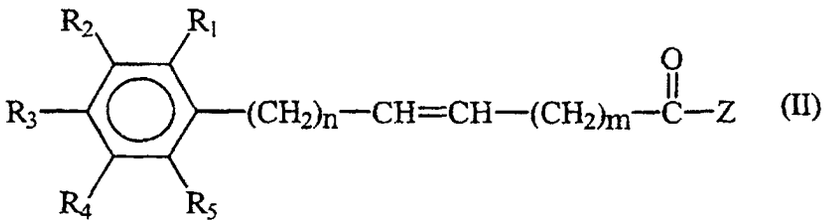
(I)

wherein:

X is selected from the group consisting of -CHCH-, -CH_2CH_2-, and -CC-;
Z is selected from the group consisting of -OH, -NH_2 and -OR_6 wherein R_6 is loweralkyl;

n and m are each at least 1 and together total an integer from 2, 3 or 4 to 6, 8, 10 or 12; and
R_1, R_2, R_3, R_4, and R_5 are each independently selected from the group consisting of -H, -OH, halo, loweralkyl, and loweralkoxy; subject to the proviso that:
a pair of R_1 and R_1, R_2 and R_3, R_3 and R_4, or R_4 and R_5 on the phenyl ring may together represent $-CR_7=CR_8-CR_9=CR_{10}-$, to form with the phenyl ring illustrated above a naphthyl ring system, wherein R_7, R_8, R_9, and R_{10} are each independently selected from the group consisting of -H, -OH, halo, loweralkyl, and loweralkoxy.

[0029] Preferred compounds of formula I above have the general formula II as given below:

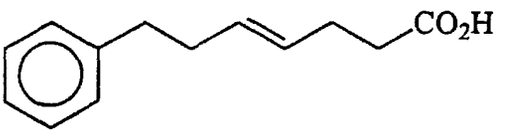


(II)

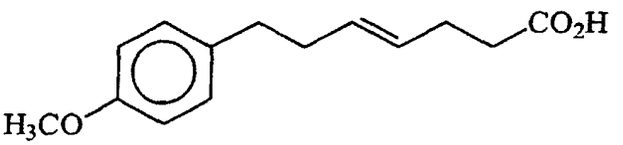
wherein Z, n, m, R_1, R_2, R_3, R_4, and R_5 are as described above. In compounds of formula II, the phenyl ring and the carbonyl carbon may be either cis (Z) or trans (E) with respect to one another. The trans configuration is preferred.

[0030] Specific examples of compounds as described above include:

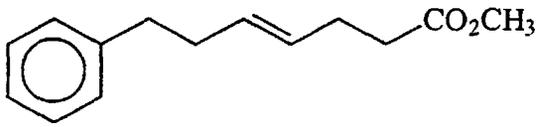
E-7-phenylhept-4-enoic acid, which has the structure:



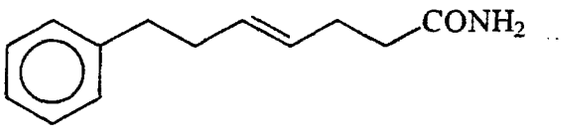
E-7-(4-methoxyphenyl)hept-4-enoic acid, which has the structure:



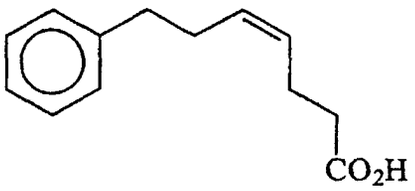
Methyl E-7-phenylhept-4-enoate, which has the structure:



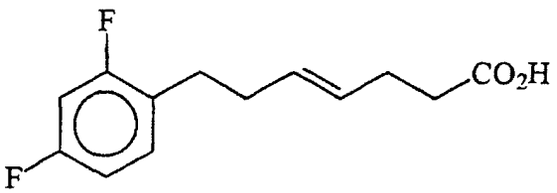
E-7-phenylhept-4-enoic acid amide, which has the structure:



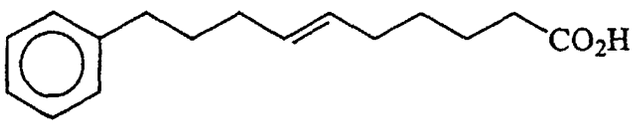
Z-7-phenylhept-4-enoic acid, which has the structure:



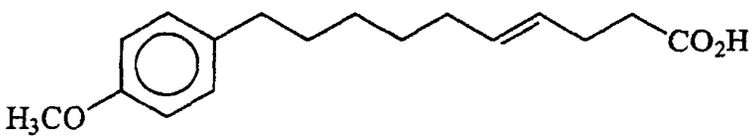
E-7-(2,4-difluorophenyl)hept-4-enoic acid, which has the structure:



E-10-phenyldec-6-enoic acid, which has the structure:



and E-10-(4-methoxyphenyl)dec-4-enoic acid, which has the structure:



[0031] Additional examples of acids of the present invention include:

E-7-(4-hydroxyphenyl)hept-4-enoic acid;
E-7-(2,4-dibromophenyl)hept-4-enoic acid;
E-7-(4-methylphenyl)hept-4-enoic acid;
E-7-(2,4-diethylphenyl)hept-4-enoic acid;
E-7-(2-ethoxyphenyl)hept-4-enoic acid;
E-7-(2,4,-dipropoxyphenyl)hept-4-enoic acid: and
E-10-(2,4-difluorophenyl)dec-4-enoic acid.

[0032] Additional examples of amides of the present invention include:

E-7-(2,4-difluorophenyl)hept-4-enoic acid amide;
E-7-(4-methoxyphenyl)hept-4-enoic acid amide;
E-10-phenyldec-6-enoic acid amide;
E-7-(2,4-difluorophenyl)dec-6-enoic acid amide;
E-7-(4-methoxyphenyl)dec-6-enoic acid amide; and

Z-7-phenylhept-4-enoic acid amide.

[0033] Additional examples of esters of the present invention include:

Methyl E-7-(2,4-difluorophenyl)hept-4-enoate;
Methyl E-7-(4-methoxyphenyl)hept-4-enoate;
Methyl E-10-phenyldec-6-enoate;
Methyl E-7-(2,4-difluorophenyl)dec-6-enoate;
Methyl E-7-(4-methoxyphenyl)dec-6-enoate;
Methyl Z-7-phenylhept-4-enoate;
Ethyl E-7-(2,4-difluorophenyl)hept-4-enoate;
Ethyl E-7-(4-methoxyphenyl)hept-4-enoate;
Ethyl E-10-phenyldec-6-enoate;
Propyl E-7-(2,4-difluorophenyl)dec-6-enoate;
Propyl E-7-(4-methoxyphenyl)dec-6-enoate;
Propyl Z-7-phenylhept-4-enoate;
Ethyl E-7-phenylhept-4-enoate;
Propyl E-7-phenylhept-4-enoate;
Butyl E-7-phenylhept 4-enoate;
Ethyl E-10-phenyldec-6-enoate;
Propyl E-10-phenyldec-6-enoate; and
Butyl E-10-phenyldec-6-enoate.

[0034] In all of the specific alkene active compounds named above, the double bond can be replaced with a single bond to produce an analogous series of active compounds that are alkanes.

[0035] In all of the specific alkene active compounds named above, the double bond can be replaced with a triple bond to produce an analogous series of active compounds that are alkynes.

[0036] In all of the specific alkene, alkane and alkyne compounds illustrated above, the phenyl ring can be replaced with a naphthyl ring to produce an analogous series of active compounds based upon a naphthyl ring system.

[0037] Compounds of the present invention can be made by the techniques described in the Examples below, or variations thereof that will be apparent to those skilled in the art.

[0038] Compounds of the present invention can be made by the technique described in M. Ansell and J. Ducker, Reduced cyclic Compounds. Part XI. The Cyclisation of ω-Arylalkenoic Acids, *J. Chem. Soc.* 206-212 (1961), or variations thereof that will be apparent to those skilled in the art.

[0039] A further aspect of the subject invention are addition salts, complexes, or prodrugs such as esters of the compounds described herein, especially the nontoxic pharmaceutically or agriculturally acceptable acid addition salts. The acid addition salts can be prepared using standard procedures in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, ethanedisulfonic or methanesulfonic acids. Esterification to form derivatives such as the methyl or ethyl esters, can also be performed using standard procedures. Tartarate salts can be prepared in accordance with standard procedures.

[0040] Also, derivation of the pesticidal compounds with long chain hydrocarbons will facilitate passage through the cuticle into the pest body cavity. Therefore, in a further embodiment, the subject invention provides compositions comprising the pesticidal compounds bound to lipids or other carriers.

2. Methods and Formulations for control of pests.

[0041] The subject invention concerns novel pest control compounds and methods for using such compounds. Specifically exemplified are novel pesticidal compounds, compositions comprising said pesticidal compounds and the use of such pesticidal compounds and compositions in controlling pests, particularly insect pests such as mosquitoes

[0042] Preferably, the subject compounds have an LD_{50} against mosquito larvae of less than 3.0 μmole/ml. More preferably, the compounds have an LD_{50} of less than 2.0 μmole/ml, and, most preferably, the compounds have an LD_{50} of less than 1.0 μmole/ml. As used herein, "LD_{50}" refers to a lethal dose of a peptide able to cause 50% mortality of larvae maintained on a diet of 1 mg/ml autoclaved yeast supplemented with the pesticidal polypeptide.

[0043] Control of pests using the pest control compounds of the subject invention can be accomplished by a variety of methods known to those skilled in the art. The plant pests that can be controlled by the compounds of the subject invention include pests belonging to the orders Coleoptera, Lepidopterans, Hemiptera and Thysanoptera. These pests all belong to the phylum Arthropod. Other pests that can be controlled according to the subject invention include members of the orders Diptera, Siphonaptera, Hymenoptera and Phthiraptera. Other pests that can be controlled by the

compounds of the subject invention include those in the family Arachnida, such as ticks, mites and spiders.

[0044] The use of the compounds of the subject invention to control pests can be accomplished readily by those skilled in the art having the benefit of the instant disclosure. For example, the compounds may be encapsulated, incorporated in a granular form, solubilized in water or other appropriate solvent, powdered, and included into any appropriate formulation for direct application to the pest or to a pest inhabited locus.

[0045] Formulated bait granules containing an attractant and the pesticidal compounds of the present invention can be applied to a pest-inhabited locus, such as to the soil. Formulated product can also be applied as a seed-coating or root treatment or total plant treatment at later stages of the crop cycle. Plant and soil treatments may be employed as wettable powders, granules or dusts, by mixing with various inert materials, such as inorganic minerals (phyllosilicates, carbonates, sulfates, phosphates, and the like) or botanical materials (powdered corncobs, rice hulls, walnut shells, and the like). The formulations may include spreader-sticker adjuvants, stabilizing agents, other pesticidal additives, or surfactants.

[0046] Liquid formulations may be aqueous-based or non-aqueous (*i.e.*, organic solvents), or combinations thereof, and may be employed as foams, gels, suspensions, emulsions, microemulsions or emulsifiable concentrates or the like. The ingredients may include rheological agents, surfactants, emulsifiers, dispersants or polymers.

[0047] As would be appreciated by a person skilled in the art, the pesticidal concentration will vary widely depending upon the nature of the particular formulation, particularly whether it is a concentrate or to be used directly. The pesticidal compound will be present in the composition by at least about 0.0001% by weight and may be 99 or 100% by weight of the total composition. The pesticidal carrier may be from 0.1 % to 99.9999% by weight of the total composition. The dry formulations will have from about 0.0001-95% by weight of the pesticide while the liquid formulations will generally be from about 0.0001-60% by weight of the solids in the liquid phase. These formulations will be administered at about 50 mg (liquid or dry) to 1 kg or more per hectare.

[0048] The formulations can be applied to the pest or the environment of the pest, e.g., soil and foliage, by spraying, dusting, sprinkling or the like.

[0049] The pest control compounds may also be provided in tablets, pellets, briquettes, bricks, blocks and the like which are formulated to float, maintain a specified depth or sink as desired. In one embodiment the formulations, according to the present invention, are formulated to float on the surface of an aqueous medium; in another embodiment they are formulated to maintain a depth of 0 to 2 feet in an aqueous medium; in yet another embodiment the formulations are formulated to sink in an aqueous environment.

3. Computational Chemistry Methods.

[0050] Methods of identifying a non-peptide TMOF agonist from a peptide TMOF agonist are a further aspect of the present invention. Such methods typically comprise the steps of:

modeling in a computer (preferably with simulated annealing) a model peptide TMOF agonist selected from the group consisting of TMOF and peptide TMOF analogs;
determining in said computer spatial orientations for at least one key feature of said model peptide compound;
generating in-said computer a putative non-peptide TMOF agonist structure, said structure including *(i)* said at least one key feature and *(ii)* spatial orientations for said at least one key feature corresponding to said spatial orientations for said at least one key feature of said model peptide compound; then
synthesizing said putative non-peptide TMOF agonist; and then
screening said putative non-peptide TMOF agonist to determine the presence of TMOF activity therein.

[0051] Peptide TMOF agonists or analogs that may be used as a basis for modeling of the instant invention include but are not limited to those disclosed in, *inter alia*, U.S. Patents Nos. 5,011,909; 5,130,253; and 5,358,934.

[0052] TMOF and other TMOF peptide agonists (preferably tripeptide fragments of TMOF) may be modeled by the INSIGHT™ software (available through the North Carolina Super Computing Center for academic use) using a simulated annealing protocol as described by Lovas and Murphy (S. Lovas and R. Murphy, Molecular Modeling of Neuropeptides, in *Neuropeptide Protocols,* pp. 209-217 (Irvine, G. B.; Williams, C. H., Eds. Humana Press, NJ. 1997)) and Damewood (J. Damewood, *Rev. Computational Chem.* **9**, 1-79 (1996). Peptide Mimetic Design with the Aid of Computational Chemistry). Composite structural data was then used to determine approximate spatial orientations for what were deemed to be key structural features, particularly as a phenyl ring and a carboxylate functional group. These data indicated a greater degree of flexibility in the N-terminus than in the C-terminus of the peptide structures. Non-peptide analogs were then subjected to energy minimization by molecular mechanics and distances between functional groups compared to the data obtained in the data set of the TMOF fragments. These data indicated a starting point for analog synthesis as exemplified by E-7-phenylhept-4-enoic acid. Actual compounds having structures corresponding to structures generated by the computational techniques are then synthesized in accordance with known tech-

niques, and screened for activity in a bioassay such as described below. Thus, compounds produced by the method that have TMOF agonist activity and can be used in the methods described herein generally have the structure P-R-C, where P is a phenyl group, R is an alkane, alkene, or alkyne, and C is a carboxylate group, all of which may be substituted or unsubstituted.

[0053] The following examples are illustrative of the practice of the present invention and should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

EXAMPLE 1

Preparation of E-7-Phenylhept-4-enoic Acid

[0054] E-7-Phenylhept-4-enoic acid was prepared from commercially available dihydrocinnamaldehyde in five steps. Dihydrocinnamaldehyde was combined with the lithium salt of ethyl diethoxyphosphonioacetate in tetrahydrofuran at room temperature. The resulting unsaturated ester, ethyl 5-phenylpent-2-enoate, was purified by chromatography. The unsaturated ester was then reduced to the allylic alcohol, E-5-phenylpent-2-en-1-ol, by reaction with excess diisobutylaluminum hydride in tetrahydrofuran at -78° C. The purified alcohol was then converted to the bromide, E-1-bromo-5-phenylpent-2-ene, by reaction with triphenylphosphine and carbon tetrabromide in methylene chloride at 0° C. The purified bromide was then used to alkylate the sodium salt of diethyl malonate to provide the diester, methyl E-1-carbomethoxy-5-phenylhept-4-enoate. The diester was purified by chromatography and then subjected to saponification using methanolic sodium hydroxide. The diacid was purified by acid/base extraction and then used directly in the next step of the reaction sequence. Decarboxylation was effected by heating the neat diacid at 170° C (under Ar) for 30 minutes. The product, E-7-phenylhept-4-enoic acid, was obtained in greater than 95% purity. Any residual diacid was removed by dissolving the acid in hexane and filtering. All compounds in the reaction sequence were fully characterized by spectral analysis (infrared and nuclear magnetic spectroscopy) and new compounds were analyzed by combustion analysis.

EXAMPLE 2

7-Phenylheptanoic Acid

[0055] 7-Phenylheptanoic acid was prepared from E-7-phenylhept-4-enoic acid by hydrogenation at 40 psi using 5% palladium on carbon as the catalyst. Quantitative conversion of the alkene to the alkane was observed by thin layer chromatographic analysis. The product acid was purified by chromatography on silica gel and fully characterized by spectroscopic methods (infrared and nuclear magnetic resonance) and combustion analysis.

EXAMPLE 3

E-7-(4-Methoxyphenyl)hept-4-enoic Acid

[0056] E-7-(4-Methoxyphenyl)hept-4-enoic acid was prepared in the same fashion as E-7-phenylhept-4-enoic acid by substituting 3-(4-methoxyphenyl) propional for dihydrocinnamaldehyde as the starting material in the synthetic sequence. 3-(4-methoxyphenyl)propional was combined with the lithium salt of ethyl diethoxyphosphonioacetate in tetrahydrofuran at room temperature. The resulting unsaturated ester, ethyl 5-(4-methoxyphenyl)pent-2-enoate, was purified by chromatography. The unsaturated ester was then reduced with excess diisobutylaluminum hydride in tetrahydrofuran at -78°C. The purified alcohol was then converted to the bromide, E-1-bromo-5-(4-methoxyphenyl)pent-2-ene, by reaction with triphenylphosphine and carbon tetrabromide in methylene chloride at 0°C. The purified bromide was then used to alkylate the sodium salt of diethyl malonate to provide the diester, methyl E-1-carbomethoxy-5-(4-methoxyphenyl)hept-4-enoate. The diester was purified by chromatography and then subjected to saponification using methanolic sodium hydroxide. The diacid was purified by acid/base extraction and then used directly in the next step of the reaction sequence. Heating the neat diacid at 170°C (under Ar) for 30 minutes effected decarboxylation. The product, E-7-(4-methoxyphenyl)hept-4-enoic acid, was obtained in greater than 95% purity. Any residual diacid was removed by dissolving the acid in hexane and filtering. All compounds in the reaction sequence were fully characterized by spectral analysis and new compounds were analyzed by combustion analysis.

EXAMPLE 4

E-7-(4-hydroxyphenyl)hept-4-enoic Acid

[0057] E-7-(4-hydroxyphenyl)hept-4-enoic acid was prepared from E-7-(4-methoxyphenyl)hept-4-enoic acid by removal of the methyl ether with boron tribromide. Boron tribromide was added to a solution of E-7-(4-methoxyphenyl) hept-4-enoic acid in methylene chloride at -78°C and stirred for four hours. The product, E-7-(4-hydroxyphenyl)hept-4-enoic acid, was obtained by aqueous work-up of the reaction mixture followed by chromatography on silica gel, and was fully characterized by spectroscopic methods (infrared and nuclear magnetic resonance) and combustion analysis.

EXAMPLE 5

Bioassay of Compounds

[0058] Mosquito larval mortality was followed for three days in microtiter plates containing 160μL sterile water, 1-4 μL of the test compound dissolved in dimethylsulfoxide, and 10 μL of 2% Brewer's yeast. Controls were run under the same conditions without the test compounds. Larval mortality in the controls was 3% for 1-3 μL dimethylsulfoxide, and up to 20% for 4 μL dimethylsulfoxide. Data for various compounds of the invention as an LD_{50} are given in **Table 1** below.

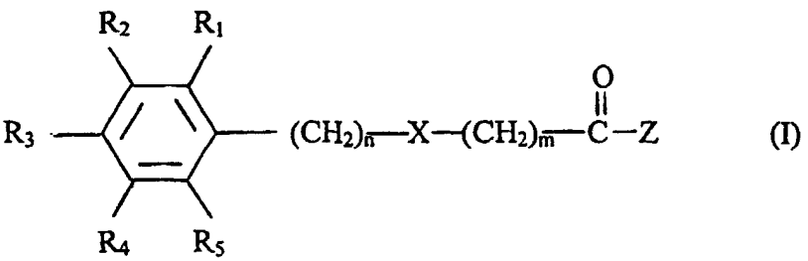
Table 1.

Bioassay of Active compounds.	
Compound	**Activity (LD_{50})**
7-Phenylheptanoic acid	0.19±0.02 mM
E-7-(4-Hydroxyphenyl)hept-4-enoic acid	0.59±0.03 mM
E-7-Phenylhept-4-enoic acid	<0.08 mM
E-7-(4-Methoxyphenyl)hept-4-enoic acid	1.28 mM

[0059] The examples and embodiments described herein are for illustrative purposes only.

Claims

1. A method for controlling a pest, comprising administering to said pest a pesticidally effective amount of a pesticidal compound of formula I:



(I)

wherein:

X is selected from -CHCH-, -CH_2CH_2, and -CC-;
Z is selected from -OH, -NH_2 and -OR_6 wherein R_6 is loweralkyl;
n and m are each at least 1 and together total an integer from 2 to 12; and
R_1, R_2, R_3 R_4 and R_5 are each independently selected from -H, -OH, halo, loweralkyl, and loweralkoxy; subject to the proviso that:

a pair of R_1 and R_1, R_2 and R_3, or R_3 and R_4 on the phenyl ring may together represent $-CR_7=CR_8-CR_9=CR_{10}-$, to form with the phenyl ring a naphthyl ring system, wherein R_7, R_8, R_9 and R_{10} are each independently selected from -H, -OH, halo, loweralkyl, and loweralkoxy.

2. A method according to claim 1, wherein R_1 is selected from hydroxy, bromo, fluoro, methyl, methoxy, propoxy, and ethoxy.

3. A method according to claim 1 or 2, wherein Z is OH or NH_2.

4. A method according to claim 1, 2 or 3, wherein at least one of R_2, R_3 or R_5 is H.

5. A method according to any preceding claim, wherein at least two of R_2, R_3 and R_5 are H.

6. A method according to any preceding claim, wherein R_2, R_3 and R_5 are all H.

7. A method according to any preceding claim, wherein R_1 is halogen or alkoxy.

8. A method according to any one of claims 1 to 5 or 7, wherein R_3 is halogen or alkoxy.

9. A method according to claim 7 or 8, wherein R_1 and R_3 are both halogen or both alkoxy.

10. A method according to claim 1, wherein said pest is an insect pest.

11. A method according to claim 10, wherein said pest is an insect selected from the group consisting of coleopterans, lepidopterans, and dipterans.

12. A method according to claim 10 or 11, wherein said pest is a blood-sucking insect.

13. A method according to claim 10, 11 or 12 wherein said pest is an insect of the suborder Nematocera.

14. A method according to any one of claims 10 to 13, wherein said pest is an insect of the family Colicidae.

15. A method according to any one of claims 10 to 14, wherein said pest is an insect of a subfamily selected from the group consisting of Culicinae, Corethrinae, Ceratopogonidae and Simuliidae.

16. A method according to claim 1, wherein said pest is an insect of a genus selected from *Culex, Theobaldia, Aedes, Anopheles, Aedes, Forciponiyia, Culicoides* and *Helea*.

17. A method according to any one of claims 10 to 16, wherein said pest is an insect species selected from *Aedes aegypti, Culex quinquefasciatus, Anopheles albimanus, Anopheles quadrimaculatus, Lutzomyia anthrophora, Culicoides variipennis, Stomoxys calcitrans, Musca domestica, Ctenocephalides feliz,* and *Heliothis virescens*.

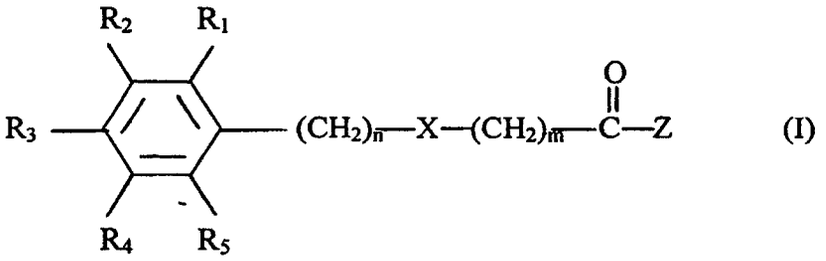
18. A method according to any one of claims 10 to 17, wherein said pest is selected from flies, fleas, ticks and lice.

19. A method according to any one of claims 10 to 17, wherein said pest is a mosquito.

20. A method according to any one of claims 10 to 17, wherein said pest is selected from beetles, caterpillars, and mites.

21. A method according to any one of claims 10 to 17, wherein said pest is selected from ants and cockroaches.

22. A method of initiating a TMOF receptor-mediated biological response, comprising contacting to a TMOF receptor *in vivo* or *in vitro* for a time and in an amount sufficient to initiate a TMOF receptor-mediated biological response a compound of Formula I:



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wherein:

X is selected from -CHCH-, -CH_2CH_2-, and -CC-;
Z is selected from -OH, -NH_2 and -OR_6 wherein R_6 is loweralkyl;
n and m are each at least 1 and together total an integer from 2 to 12; and
R_1, R_2, R_3, R_4, and R_5 are each independently selected from -H, -OH, halo, loweralkyl, and loweralkoxy; subject to the proviso that:

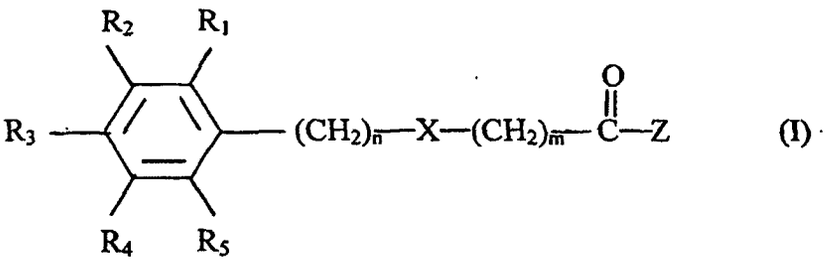
a pair of R_1 and R_1, R_2 and R_3, or R_3 and R_4 on the phenyl ring may together represent -CR_7=CR_8-CR_9=CR_{10}-, to form with the phenyl ring a naphthyl ring system, wherein R_7, R_8, R_9, and R_{10} are each independently selected from -H, -OH, halo, loweralkyl, and loweralkoxy.

23. A method according to claim 22, wherein said biological response is inhibition of biosynthesis of a digestive enzyme.

24. A method according to claim 23, wherein said digestive enzyme is trypsin.

25. A method according to claim 22, 23 or 24, wherein said contacting step is carried out *in vivo* in an insect pest.

26. A pest control composition comprising a pesticidal carrier and a pesticidal compound of Formula I:



(I)

wherein:

X is selected from -CHCH-, -CH_2CH_2-, and -CC-;
Z is selected from -OH, -NH_2 and -OR_6 wherein R_6 is loweralkyl;
n and m are each at least 1 and together total an integer from 2, 3 or 4 to 6, 8, 10 or 12; and
R_1, R_2, R_3, R_4, and R_5 are each independently selected from -H, -OH, halo, loweralkyl, and loweralkoxy; subject to the proviso that:

a pair of R_1 and R_1, R_2 and R_3, or R_3 and R_4 on the phenyl ring may together represent -CR_7=CR_8-CR_9=CR_{10}-, to form with the phenyl ring a naphthyl ring system, wherein R_7, R_8, R_9, and R_{10} are each independently selected from -H, -OH, halo, loweralkyl, and loweralkoxy.

27. A composition according to claim 26, wherein said composition is a liquid composition.

28. A composition according to claim 26 or 27, wherein said pesticidal carrier comprises an aqueous solution.

29. A composition according to claim 26 or 27, wherein said pestdicidal carrier comprises an organic solvent.

30. A composition according to any one of claims 26 to 29, wherein said pesticidal carrier comprises an emulsion.

31. A composition according to claim 26, wherein said composition is a solid composition.

32. A composition according to claim 31, wherein said composition is a bait granule.

33. A composition according to any one of claims 26 to 32, wherein said compound of Formula I is selected from: E-7-phenylhept-4-enoic acid; E-7-(4-methoxyphenyl)hept-4-enoic acid; Methyl E-7-phenylhept-4-enoate; E-7-phenylhept-4-enoic acid amide; Z-7-phenylhept-4-enoic acid; E-7-(2,4-difluorophenyl)hept-4-enoic acid; E-10-phenyldec-6-enoic acid; E-1-(4-methoxyphenyl)dec-4-enoic acid; E-7-(4-hydroxyphenyl)hept-4-enoic acid; E-7-(2,4-dibromophenyl)hept-4-enoic acid; E-7-(4-methylphenyl)hept-4-enoic acid; E-7-(2,4-diethylphenyl)hept-4-enoic acid; E-7-(2-ethoxyphenyl)hept-4-enoic acid; E-7-(2,4,-dipropoxyphenyl)hept-4-enoic acid; E-10-(2,4-difluorophenyl) dec-4-enoic acid; E-7-(2,4-difluorophenyl)hept-4-enoic acid amide; E-7-(4-methoxyphenyl)hept-4-enoic acid amide; E-10-phenyldec-6-enoic acid amide; E-7-(2,4-difluorophenyl)dec-6-enoic acid amide; E-7-(4-methoxyphenyl)dec-6-enoic acid amide; Z-7-phenylhept-4-enoic acid amide; Methyl E-7-(2,4-difluorophenyl)hept-4-enoate; Methyl E-7-(4-methoxyphenyl)hept-4-enoate; Methyl E-10-phenyldec-6-enoate; Methyl E-7-(2,4-difluorophenyl) dec-6-enoate; Methyl E-7-(4-methoxyphenyl)dec-6-enoate; Methyl Z-7-phenylhept-4-enoate; Ethyl E-7-(2,4-difluorophenyl)hept-4-enoate; Ethyl E-7-(4-methoxyphenyl)hept-4-enoate; Ethyl E-10-phenyldec-6-enoate; Propyl E-7-(2,4-difluorophenyl)dec-6-enoate; Propyl E-7-(4-methoxyphenyl)dec-6-enoate; Propyl Z-7-phenylhept-4-enoate; Ethyl E-7-phenylhept-4-enoate; Propyl E-7-phenylhept-4-enoate; Butyl E-7 phenylhept-4-enoate; Ethyl E-10-phenyldec-6-enoate; Propyl E-10-phenyldec-6-enoate; and Butyl E-10-phenyldec-6-enoate.

34. A method according to any one of claims 1 to 21 wherein said compound of formula I is selected from the compounds as claimed in claim 33.

35. A method of identifying a non-peptide TMOF agonist from a peptide TMOF agonist, said method comprising the steps of:

modelling in a computer a model peptide TMOF agonist selected from the group consisting of TMOF and peptide TMOF analogs;
determining in said computer spatial orientations for at least one key feature of said model peptide compound;
generating in said computer a putative non-peptide TMOF agonist structure, said structure including *(i)* said at least one key feature and *(ii)* spatial orientations for said at least one key feature corresponding to said spatial orientations for said at least one key feature of said model peptide compound; then
synthesising said putative non-peptide TMOF agonist; and then screening said putative non-peptide TMOF agonist to determine the presence of TMOF activity therein.

36. A method according to claim 35, wherein said modelling step is carried out with simulated annealing.

37. A method according to claim 35 or 36, wherein said screening step is carried out *in vivo* on insects.

38. A method according to any one of claims 35 to 37, wherein said at least one key feature of said non-peptide TMOF agonist structure comprises *(i)* a phenyl ring, and *(ii)* a carboxylate functional group.

39. A method of controlling a pest, comprising administering to said pest a pesticidally effective amount of a non-peptide TMOF analog.

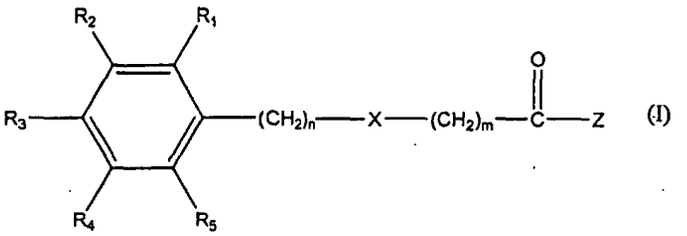
40. A method according to claim 39, wherein said non-peptide TMOF analog is an organic compound that has TMOF activity.

41. A method according to claim 40, wherein said organic compound that has TMOF activity includes *(i)* a phenyl group, and *(ii)* a carboxylate group.

42. A method according to claim 40 or 41, wherein said organic compound has the structure P-R-C, where P is a phenyl group, R is an alkane, alkene, or alkyne, and C is a carboxylate group.

Patentansprüche

1. Verfahren zur Bekämpfung eines Schädlings, das die Verabreichung einer pestizid wirksamen Menge einer pestiziden Verbindung der Formel I an diesen Schädling umfasst:



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worin:

X ausgewählt ist aus -CHCH-, CH_2CH_2 und -CC-;
Z ist ausgewählt aus -OH, $-NH_2$ und $-OR_6$ worin R_6 niedriges Alkyl ist;
n und m sind jeweils mindestens 1 und zusammen insgesamt eine ganze Zahl von 2 bis 12 und
R_1, R_2, R_3, R_4 und R_5 sind jeweils unabhängig voneinander ausgewählt aus -H, -OH, Halogen, niedrigem Alkyl und niedrigem Alkoxy; unter der Voraussetzung, dass:

ein Paar aus R_1 und R_1, R_2 und R_3 oder R_3 und R_4 am Phenylring zusammen $-CR_7=CR_8-CR_9=CR_{10}-$ darstellen können, um mit dem Phenylring ein Naphthalin-Ringsystem zu bilden, worin R_7, R_8, R_9 und R_{10} jeweils unabhängig voneinander ausgewählt sind aus -H, -OH, Halogen, niedrigem Alkyl und niedrigem Alkoxy.

2. Verfahren gemäß Anspruch 1, worin R1 ausgewählt ist aus Hydroxy, Brom, Fluor, Methyl, Methoxy, Propoxy und Ethoxy.

3. Verfahren gemäß Anspruch 1 oder 2, worin Z OH oder NH_2 ist.

4. Verfahren gemäß Anspruch 1, 2 oder 3, worin wenigstens einer der Reste von R_2, R_3 oder R_5 H ist.

5. Verfahren gemäß irgendeinem vorangehenden Anspruch, worin wenigstens zwei der Reste von R_2, R_3 und R_5 H sind.

6. Verfahren gemäß irgendeinem vorangehenden Anspruch, worin alle Reste R_2, R_3 und R_5 H sind.

7. Verfahren gemäß irgendeinem vorangehenden Anspruch, worin R_1 Halogen oder Alkoxy ist.

8. Verfahren gemäß irgendeinem der Ansprüche 1 bis 5 oder 7, worin R_3 Halogen oder Alkoxy ist.

9. Verfahren gemäß Anspruch 7 oder 8, worin R_1 und R_3 beide Halogen oder beide Alkoxy sind.

10. Verfahren gemäß Anspruch 1, worin dieser Schädling ein Schadinsekt ist.

11. Verfahren gemäß Anspruch 10, worin dieser Schädling ein Schadinsekt ist, ausgewählt aus der Gruppe bestehend aus Coleoptera, Lepidoptera und Diptera.

12. Verfahren gemäß Anspruch 10 oder 11, worin dieser Schädling ein blutsaugendes Insekt ist.

13. Verfahren gemäß Anspruch 10, 11 oder 12, worin dieser Schädling ein Insekt der Unterordnung Nematocera ist.

14. Verfahren gemäß irgendeinem der Ansprüche 10 bis 13, worin dieser Schädling ein Insekt der Familie Colicidae ist.

15. Verfahren gemäß irgendeinem der Ansprüche 10 bis 14, worin dieser Schädling ein Insekt der Unterfamilie, ausgewählt aus der Gruppe bestehend aus Culicinae, Corethrinae, Ceratopogonidae und Simuliidae ist.

16. Verfahren gemäß Anspruch 1, worin dieser Schädling ein Insekt der Gattung, ausgewählt aus *Culex, Theobaldia, Aedes, Anopheles, Aedes, Forciponiyia, Culicoldes* und *Helea* ist.

17. Verfahren gemäß irgendeinem der Ansprüche 10 bis 16, worin dieser Schädling eine Insektenart, ausgewählt aus *Aedes aegypti, Culex quinquefasciatus, Anopheles albimanus, Anopheles quadrimaculatus, Lutzomyia anthrophora, Culicoides variipennis, Stomoxys calcitrans, Musca domestica, Ctenocephalides feliz* und *Heliothis virescens* ist.

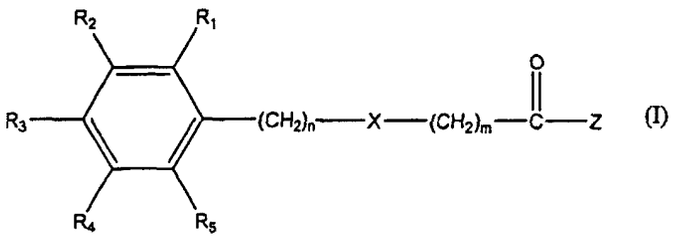
18. Verfahren gemäß irgendeinem der Ansprüche 10 bis 17, worin dieser Schädling ausgewählt ist aus Fliegen, Flöhen, Zecken und Läusen.

19. Verfahren gemäß irgendeinem der Ansprüche 10 bis 17, worin dieser Schädling ein Moskito ist.

20. Verfahren gemäß irgendeinem der Ansprüche 10 bis 17, worin dieser Schädling ausgewählt ist aus Käfern, Raupen und Milben.

21. Verfahren gemäß irgendeinem der Ansprüche 10 bis 17, worin dieser Schädling ausgewählt ist aus Ameisen und Schaben.

22. Verfahren zur Auslösung einer TMOF-Rezeptor-vermittelten biologischen Antwort, die das Inkontaktbringen eines TMOF-Rezeptors *in vivo* oder *in vitro* mit einer Verbindung der Formel I für eine Zeit und in einer Menge umfasst, die ausreichend sind, eine TMOF-Rezeptor-vermittelten biologischen Antwort auszulösen:



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worin:

X ausgewählt ist aus -CHCH-, CH_2CH_2 und -CC-;
Z ist ausgewählt aus -OH, $-NH_2$ und $-OR_6$ worin R_6 niedriges Alkyl ist;
n und m sind jeweils mindestens 1 und zusammen insgesamt eine ganze Zahl von 2 bis 12 und
R_1, R_2, R_3, R_4 und R_5 sind jeweils unabhängig voneinander ausgewählt aus -H, -OH, Halogen, niedrigem Alkyl und niedrigem Alkoxy; unter der Voraussetzung, dass:

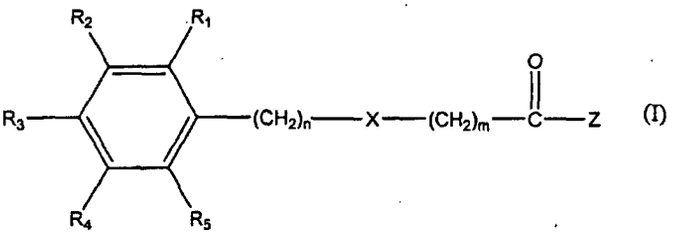
ein Paar aus R_1 und R_1, R_2 und R_3 oder R_3 und R_4 am Phenylring zusammen $-CR_7=CR_8-CR_9=CR_{10}-$ darstellen können, um mit dem Phenylring ein Naphthalin-Ringsystem zu bilden, worin R_7, R_8, R_9 und R_{10} jeweils unabhängig voneinander ausgewählt sind aus -H, -OH, Halogen, niedrigem Alkyl und niedrigem Alkoxy.

23. Verfahren gemäß Anspruch 22, worin diese biologische Antwort die Hemmung der Biosynthese eines Verdauungsenzyms ist.

24. Verfahren gemäß Anspruch 23, worin dieses Verdauungsenzym Trypsin ist.

25. Verfahren gemäß Anspruch 22, 23 oder 24, worin der Schritt des Inkontaktbringens *in vivo* in einem Schadinsekt durchgeführt wird.

26. Schädlingsbekämpfungszusammensetzung, die einen pestiziden Träger und eine pestizide Verbindung der Formel I umfasst:



worin:

X ausgewählt ist aus -CHCH-, CH_2CH_2 und -CC-;
Z ist ausgewählt aus -OH, $-NH_2$ und $-OR_6$ worin R_6 niedriges Alkyl ist;
n und m sind jeweils mindestens 1 und zusammen insgesamt eine ganze Zahl von 2, 3 oder 4 bis 6, 8, 10 oder 12 und
R_1, R_2, R_3, R_4 und R_5 sind jeweils unabhängig voneinander ausgewählt aus -H, -OH, Halogen, niedrigem Alkyl und niedrigem Alkoxy; unter der Voraussetzung, dass:

ein Paar aus R_1 und R_1, R_2 und R_3 oder R_3 und R_4 am Phenylring zusammen $-CR_7=CR_8-CR_9=CR_{10}-$ darstellen können, um mit dem Phenylring ein Naphthalin-Ringsystem zu bilden, worin R_7, R_8, R_9 und R_{10} jeweils unabhängig voneinander ausgewählt sind aus -H, -OH, Halogen, niedrigem Alkyl und niedrigem Alkoxy.

27. Zusammensetzung gemäß Anspruch 26, worin diese Zusammensetzung eine flüssige Zusammensetzung ist.

28. Zusammensetzung gemäß Anspruch 26 oder 27, worin dieser pestizide Träger eine wässrige Lösung umfasst.

29. Zusammensetzung gemäß Anspruch 26 oder 27, worin dieser pestizide Träger ein organisches Lösemittel umfasst.

30. Zusammensetzung gemäß irgendeinem der Ansprüche 26 bis 29, worin dieser pestizide Träger eine Emulsion umfasst.

31. Zusammensetzung gemäß Anspruch 26, worin diese Zusammensetzung eine feste Zusammensetzung ist.

32. Zusammensetzung gemäß Anspruch 31, worin diese Zusammensetzung ein Köder-Körnchen ist.

33. Zusammensetzung gemäß irgendeinem der Ansprüche 26 bis 32, worin die genannte Verbindung der Formel I ausgewählt ist aus: E-7-Phenylhept-4-ensäure; E-7-(4-methoxyphenyl)hept-4-ensäure; Methyl-E-7-phenylhept-4-enoat; E-7-Phenylhept-4-ensäure; Z-7-Phenylhept-4-ensäure; E-7-(2,4-Difluorphenyl)hept-4-ensäure; E-10-Phenyldec-6-ensäure; E-1-(4-Methoxyphenyl)dec-4-ensäure; E-7-(4-Hydroxyphenyl)hept-4-ensäure; E-7-(2,4-Dibromphenyl)hept-4-ensäure; E-7-(4-Methylphenyl)hept-4-ensäure; E-7-(2,4-Diethylphenyl)hept-4-ensäure; E-7-(2-Ethoxyphenyl)hept-4-ensäure; E-7-(2,4-Dipropoxyphenyl)hept-4-ensäure; E-10-(2,4-Difluorphenyl)dec-4-ensäure; E-7-(2,4-Difluorphenyl)hept-4-ensäureamid; E-7-(4-Methoxyphenyl)hept-4-ensäureamid; E-10-Phenyldec-6-ensäureamid; E-7-(2,4-Difluorphenyl)dec-6-ensäureamid; E-7-(4-Methoxyphenyl)dec-6-ensäureamid; Z-7-Phenylhept-4-ensäureamid; Methyl-E-7-(2,4-difluorphenyl)hept-4-enoat; Methyl-E-7-(4-methoxyphenyl)hept-4-enoat; Methyl-E-10-phenyldec-6-enoat; Methyl-E-7-(2,4-difluorphenyl)dec-6-enoat; Methyl-E-7-(4-methoxyphenyl)dec-6-enoat; Methyl-Z-7-phenylhept-4-enoat; Ethyl-E-7-(2,4-difluorphenyl)hept-4-enoat; Ethyl-E-7-(4-methoxyphenyl)hept-4-enoat; Ethyl-E-10-phenyldec-6-enoat; Propyl-E-7-(2,4-difluorphenyl)dec-6-enoat; Propyl-E-7-(4-methoxyphenyl)dec-6-enoat; Propyl-Z-7-phenylhept-4-enoat; Ethyl-E-7-phenylhept-4-enoat; Propyl-E-7-phenylhept-4-enoat; Butyl-E-7-phenylhept-4-enoat; Ethyl-E-10-phenyldec-6-enoat; Propyl-E-10-phenyldec-6-enoat und Butyl-E-10-phenyldec-6-enoat.

34. Verfahren gemäß irgendeinem der Ansprüche 1 bis 21, worin diese Verbindung der Formel I ausgewählt ist aus den in Anspruch 33 beanspruchten Verbindungen.

35. Verfahren zur Identifizierung eines nicht-peptidischen TMOF-Agonisten aus einem peptidischen TMOF-Agonisten, wobei dieses Verfahren die Schritte umfasst der:

Modellierung eines Modells eines peptidischen TMOF-Agonisten mit einem Computer, welcher ausgewählt wird aus der Gruppe bestehend aus TMOF und peptidischen TMOF-Analogen;
Bestimmung der räumlichen Orientierungen für wenigstens ein Schlüsselmerkmal dieser peptidischen Modellverbindung mit diesem Computer;
Erzeugung einer putativen nicht-peptidischen TMOF-Agonist-Struktur mit diesem Computer, wobei diese-Struktur (i) dieses wenigstens eine Schlüsselmerkmal und (ii) räumliche Orientierungen für dieses wenigstens eine Schlüsselmerkmal einschließt, die mit den räumlichen Orientierungen des genannten wenigstens einen Schlüsselmerkmals der peptidischen Modellverbindung korrespondieren; dann
Synthetisieren dieses putativen nicht-peptidischen TMOF-Agonisten und dann Screening dieses putativen nicht-peptidischen TMOF-Agonisten, um darin dessen TMOF-Aktivität zu bestimmen.

36. Verfahren gemäß Anspruch 35, worin dieser Modellierungsschritt mit simuliertem Annealing durchgeführt wird.

37. Verfahren gemäß Anspruch 35 oder 36, worin dieser Screeningschritt in vivo an Insekten durchgeführt wird.

38. Verfahren gemäß irgendeinem der Ansprüche 35 bis 37, worin dieses mindestens eine Schlüsselmerkmal dieser nicht-peptidischen TMOF-Agonist-Struktur (i) einen Phenylring und (ii) eine funktionelle Carboxylatgruppe umfasst.

39. Verfahren zur Bekämpfung eines Schädlings, das die Verabreichung einer pestizid wirksamen Menge eines nicht-peptidischen TMOF-Analogen an einen Schädling umfasst.

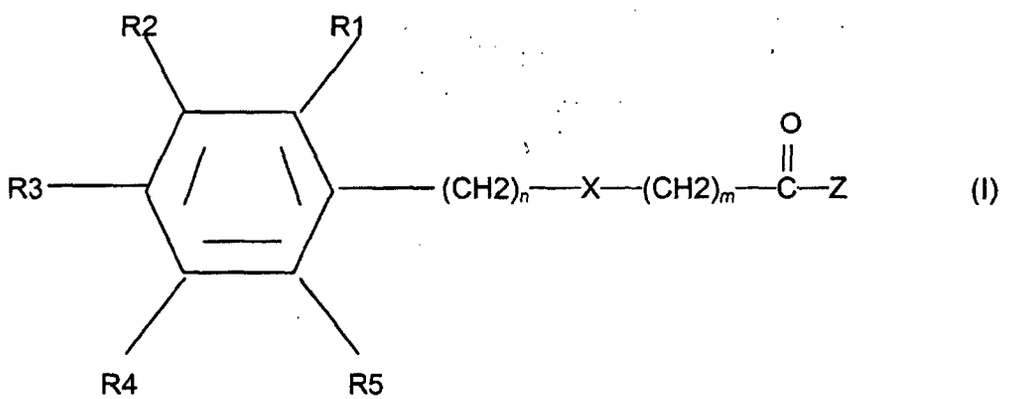
40. Verfahren gemäß Anspruch 39, worin dieser nichtpeptidische TMOF-Analoge eine organische Verbindung ist, die TMOF-Aktivität besitzt.

41. Verfahren gemäß Anspruch 40, worin diese organische Verbindung, welche TMOF-Aktivität besitzt, (i) eine Phenylgruppe und (ii) eine Carboxylatgruppe einschließt.

42. Verfahren gemäß Anspruch 40 oder 41, worin diese organische Verbindung die Struktur P-R-C besitzt, worin P ein Phenyl ist, R ein Alkan, Alken oder Alkin ist und C eine Carboxylatgruppe ist.

Revendications

1. Méthode de contrôle de déprédateurs, comprenant l'administration audit déprédateur d'une quantité efficace anti-parasitaire d'un composé anti-parasitaire de formule I :



(I)

caractérisée en ce que :

- X est choisi parmi -CHCH-, -CH_2CH_2, et -CC ;
- Z est choisi parmi -OH, -NH_2 et -OR_6 où R_6 est un alkyle faible ;
- n et m sont, chacun, au moins égaux à 1 et représentent ensemble un nombre entier variant de 2 à12 ; et
- R_1, R_2, R_3, R_4 et R_5 sont, chacun, choisis de manière indépendante parmi -H, -OH, halo, alkyle faible et alkoxy faible ; soumis à la clause conditionnelle que :

une paire de R_1 et R_1, R_2, et R_3, ou R_3 et R_4, sur le cycle phényl peut représenter ensemble $-CR_7=CR_8-CR_9=CR_{10}$, pour former avec le cycle phényl un système de cycle naphtyl, **caractérisée en ce que** R_7, R_8, R_9, et R_{10} sont, chacun, choisis de manière indépendante parmi -H, -OH, halo, alkyl faible et alkoxy faible.

2. Méthode selon la revendication 1, **caractérisée en ce que** R_1 est choisi parmi hydroxy, bromo, fluoro, méthyle, méthoxy, propoxy, et ethoxy.

3. Méthode selon la revendication 1 ou 2, **caractérisée en ce que** Z est OH ou NH_2.

4. Méthode selon la revendication 1, 2 ou 3, **caractérisée en ce qu'**au moins un de R_2, R_3 ou R_5 est H.

5. Méthode selon l'une des revendications précédentes, **caractérisée en ce qu'**au moins deux de R_2, R_3 et R_5 sont H.

6. Méthode selon l'une des revendications précédentes, **caractérisée en ce que** R_2, R_3 et R_5 sont tous H.

7. Méthode selon l'une des revendications précédentes, **caractérisée en ce que** R_1 est halogène ou alkoxy.

8. Méthode selon l'une des revendications 1 à 5 ou 7, **caractérisé en ce que** R_3 est halogène ou alkoxy.

9. Méthode selon la revendication 7 ou 8, **caractérisé en ce que** R_1 et R_3 sont tous deux halogènes ou tous deux alkoxy.

10. Méthode selon la revendication 1, **caractérisé en ce que** ledit déprédateur est un insecte nuisible.

11. Méthode selon la revendication 10, **caractérisée en ce que** ledit déprédateur est un insecte choisi parmi le groupe comprenant les coléoptères, lépidoptères et diptères.

12. Méthode selon la revendication 10 ou 11, **caractérisée en ce que** ledit déprédateur est un insecte suceur de sang.

13. Méthode selon la revendication 10, 11 ou 12, **caractérisée en ce que** ledit déprédateur est un insecte du sous-ordre des Nématocères.

14. Méthode selon l'une des revendications 10 à 13, **caractérisée en ce que** ledit déprédateur est un insecte de la famille des Colicidae.

15. Méthode selon l'une des revendications 10 à 14, **caractérisée en ce que** ledit déprédateur est un insecte d'une sous-famille choisie parmi le groupe comprenant les Culicinae, Corethrinae, Ceratopogonidae et Simuliidae.

16. Méthode selon la revendication 1, **caractérisée en ce que** ledit déprédateur est un insecte d'un genre choisi parmi *Culex, Theoaldia, Aedes, Anopheles, Aedes, Forciponiyia, Culicoides et Helea*.

17. Méthode selon l'une des revendications 6 à 16, **caractérisée en ce que** ledit déprédateur est une espèce d'insectes choisis parmi *Aedes aegypti, Culex quinquefasciatus. Anopheles albimanus, Anopheles quadrimaculatus, Lutzomyia anthrophora, Culicoides variipennis, Stomoxys calcitrans, Musca domestica, Ctenocephalides feliz, et Heliothis virescens.*

18. Méthode selon l'une des revendications 10 à 17, **caractérisée en ce que** ledit déprédateur est choisi parmi les mouches, puces, tiques et poux.

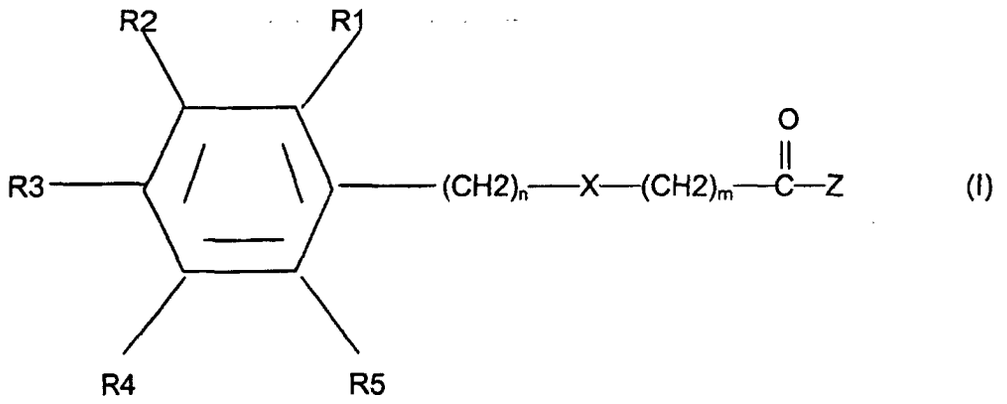
19. Méthode selon l'une des revendications 10 à 17, **caractérisée en ce que** ledit déprédateur est un moustique.

20. Méthode selon l'une des revendications 10 à 17, **caractérisée en ce que** ledit déprédateur est choisi parmi les coléoptères, chenilles, et acariens.

21. Méthode selon l'une des revendications 10 à 17, **caractérisée en ce que** ledit déprédateur est choisi par les fourmis et les blattes.

22. Méthode d'initiation d'une réponse biologique assistée par récepteur TMOF, comprenant la mise en contact sur

un récepteur TMOF *in vivo* ou *in vitro* pour un temps et dans une quantité suffisante pour initier une réponse biologique assistée par récepteur TMOF, d'un composé de formule I :



(I)

caractérisée en ce que :

- X est choisi parmi -CHCH-, $-CH_2CH_2$, et -CC ;
- Z est choisi parmi -OH, $-NH_2$ et $-OR_6$ où R_6 est un alkyl faible ;
- n et m sont, chacun, au moins égaux à 1 et représentent ensemble un nombre entier variant de 2 à12 ; et
- R_1, R_2, R_3, R_4 et R_5 sont, chacun, choisis de manière indépendante parmi -H, -OH, halo, alkyl faible et alkoxy faible ; soumis à la clause conditionnelle que :

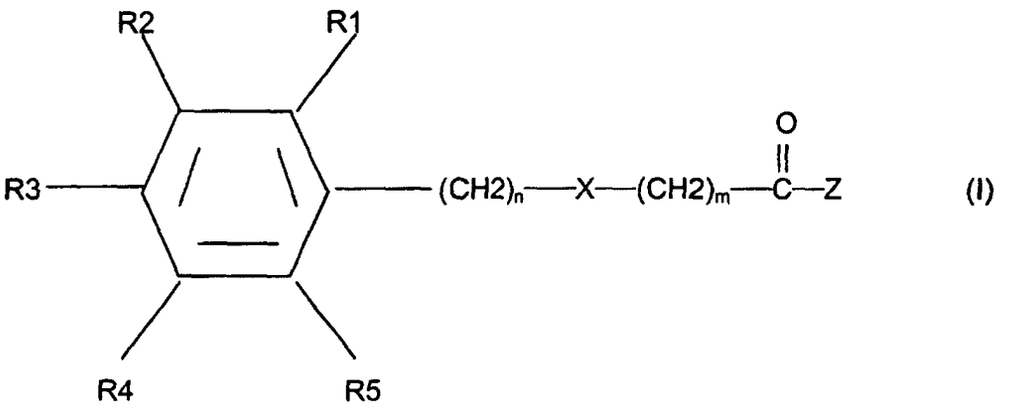
une paire de R_1 et R_1, R_2, et R_3, ou R_3 et R_4, sur le cycle phényle peut représenter ensemble $-CR_7=CR_8-CR_9=CR_{10}-$, pour former avec le cycle phényl un système de cycle naphtyl, **caractérisée en ce que** R_7, R_8, R_9, et R_{10} sont, chacun, choisis de manière indépendante parmi -H, -OH, halo, alkyl faible et alkoxy faible.

23. Méthode selon la revendication 22, **caractérisée en ce que** ladite réponse biologique est l'inhibition de biosynthèse d'une enzyme digestive.

24. Méthode selon la revendication 23, **caractérisée en ce que** ladite enzyme digestive est la trypsine.

25. Méthode selon la revendication 22, 23 ou 24, **caractérisée en ce que** ladite étape de mise en contact est réalisée *in vivo* dans un insecte nuisible.

26. Composition de contrôle de déprédateurs comprenant un porteur anti-parasitaire et un composé anti-parasitaire de formule I :



(I)

caractérisée en ce que :

- X est choisi parmi -CHCH-, -CH_2CH_2, et -CC ;
- Z est choisi parmi -OH, -NH_2 et -OR_6 où R_6 est un alkyl faible ;
- n et m sont, chacun, au moins égaux à 1 et représentent ensemble un nombre entier valant 2, 3 ou 4 à 6, 8, 10 ou 12 ; et
- R_1, R_2, R_3, R_4 et R_5 sont, chacun, choisis de manière indépendante parmi -H, -OH, halo, alkyl faible et alkoxy faible ; soumis à la clause conditionnelle que :

une paire de R_1 et R_1, R_2, et R_3, ou R_3 et R_4, sur le cycle phényle peut représenter ensemble -CR_7=CR_8-CR_9=CR_{10}-, pour former avec le cycle phényle un système de cycle naphtyl, **caractérisée en ce que** R_7, R_8, R_9, et R_{10} sont, chacun, choisis de manière indépendante parmi -H, -OH, halo, alkyl faible et alkoxy faible.

27. Composition sur la revendication 26, **caractérisée en ce que** ladite composition est une composition liquide.

28. Composition selon la revendication 26 ou 27, **caractérisée en ce que** ledit porteur anti-parasitaire comprend une solution aqueuse.

29. Composition selon la revendication 26 ou 27, **caractérisée en ce que** ledit porteur anti-parasitaire comprend un solvant organique.

30. Composition selon l'une des revendications 26 à 29, **caractérisée en ce que** ledit porteur anti-parasitaire comprend une émulsion.

31. Composition selon la revendication 26, **caractérisée en ce que** ladite composition est une composition solide.

32. Composition selon la revendication 31, **caractérisée en ce que** ladite composition est un granulé d'appât.

33. Composition selon l'une des revendications 26 à 32, **caractérisée en ce que** ledit composé de formule I est choisi parmi : acide E-7-phénylhept-4-énoïque ; acide E-7-(4-méthoxyphényl)hept-4-énoïque ; E-7-phenylhept-4-énoate de méthyl ; amide d'acide E-7-phénylhept-4-énoïque ; acide Z-7-phenylhept-4-énoïque ; acide E-7-(2,4-difluorophényl)hept-4-énoïque ; acide E-10-phényldec-6-énoïque ; acide E-1-(4-méthoxyphényl)dec-4-énoïque ; acide E-7(4-hydroxyphényl)hept-4-énoïque ; acide E-7-(2,4-dibromophényl)hept-4-énoïque ; acide E-7-(4-méthylphényl) hept-4-énoïque; acide E-7-(2,4-diéthylphényl)hept-4-énoïque ; acide E-7-(2-éthoxyphényl)hept-4-énoïque ; acide E-7-(2,4-dipropoxyphényl)hept-4-énoïque; acide E-10-(2,4-difluorophényl)dec-4-énoïque ; amide d'acide E-7-(2,4-difluorophényl)hept-4 énoïque ; amide d'acide E-7-(4-méthoxyphényl)hept-4-énoïque ; amide d'acide E-10-phényldec-6-énoïque ; amide d'acide E-7-(2,4-difluorophényl)dec-6-énoïque ; E-7-(4-méthoxyphényl)dec-6-énoïque ; amide d'acide Z-7-phénylhept-4-énoïque ; E-7-(2,4-difluorophényl)hept-4-énoate de méthyl ; E-7-(4-méthoxyphényl)hept-4-énoate de méthyl ; E-10-phényldec-6-énoate de méthyl ; E-7-(2,4-difluorophényl)dec-6-énoate de méthyl; E-7-(4-méthoxyphényl)dec6-énoate de méthyl ; Z-7-phénylhept-4-énoate de méthyl ; E-7-(2,4-difluorophényl)hept-4-énoate d'éthyl ; E-7-(4-méthoxyphényl)hept-4-énoate d'éthyl; E-10-phenyldec-6-énoate d'éthyl ; E-7-(2,4-difluorophényl)dec-6-énoate de propyl ; E-7-(4-méthoxyphényl)dec-6-énoate de propyl ; Z-7-phenylhept-4-énoate de propyl ; E-7-phénylhept-4-énoate d'éthyl ; E-7-phenylhept-4-énoate de propyl ; E-7-phénylhept-4-énoate de butyl ; E-10-phenyldec-6-énoate d'éthyl ; E-10-phényldec-6-énoate de propyl; et E-10-phényldec-6-énoate de butyl.

34. Méthode selon l'une des revendications 1 à 21, **caractérisée en ce que** ledit composé de formule I est choisi parmi les composés, comme revendiqué dans la revendication 33.

35. Méthode d'identification d'un agoniste TMOF non peptide à partir d'un agoniste TMOF peptide, ladite méthode comprenant les étapes de :

- modélisation par ordinateur d'un agoniste TMOF peptide modèle, choisi parmi le groupe comprenant les analogues TMOF et TMOF peptide ;
- détermination dans ledit ordinateur des orientations spatiales pour au moins une caractéristique déterminante dudit composé peptide modèle ;
- génération dans ledit ordinateur d'une structure agoniste TMOF non peptide putative, ladite structure incluant (*i*), ladite au moins une caractéristique déterminante et (*ii*) les orientations spatiales pour ladite au moins une

caractéristique déterminante correspondant auxdites orientations spatiales pour ladite au moins une caractéristique déterminante dudit composé peptide modèle ; ensuite

- la synthèse dudit agoniste TMOF non peptide putatif ; et ensuite
- le criblage dudit agoniste TMOF non peptide putatif pour déterminer la présence d'activité TMOF dedans.

36. Méthode selon la revendication 35, **caractérisée en ce que** ladite étape de modélisation est réalisée par annelage simulé.

37. Méthode selon la revendication 35 ou 36, **caractérisée en ce que** ladite étape de criblage est réalisée *in vivo* sur des insectes.

38. Méthode selon l'une des revendications 35 à 37, **caractérisée en ce que** ladite au moins une caractéristique déterminante de ladite structure agoniste TMOF non peptide comprend (*i*) un cycle phényl, et (*ii*) un groupe fonctionnel carboxylate.

39. Méthode de contrôle des déprédateurs comprend l'administration audit déprédateur d'une quantité efficace antiparasitaire d'un analogue TMOF non peptide.

40. Méthode selon la revendication 39, **caractérisée en ce que** ledit analogue TMOF non peptide est un composé organique qui a une activité TMOF.

41. Méthode selon la revendication 40, **caractérisée en ce que** ledit composé organique qui a une activité TMOF inclut (*i*) un groupe phényl, et (*ii*) un groupe carboxylate.

42. Méthode selon la revendication 40 ou 41, **caractérisée en ce que** ledit composé organique a la structure P-R-C, où P est un groupe phényl, R est un alcane, alcène ou alcyne, et C est un groupe carboxylate.